REMARKS

Applicants wish to express their appreciation to the Examiner that claim 15 is free of prior art and has been allowed.

Claims 1-7 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,399,649.

Applicant is filing an unexecuted terminal disclaimer herewith; the executed terminal disclaimer will be filed by supplemental amendment. Accordingly, the rejection of claims 1-7 has been completely obviated, and its withdrawal is respectfully requested.

Claims 1-7 were rejected under 35 U.S.C. § 112, first paragraph.

Applicant respectfully submits that this rejection should be withdrawn for the following reasons.

Applicant appreciates the Examiner's indication that the specification enables administration of two PDE4 inhibitors for the treatment of chronic lymphocytic leukemia (CLL), namely rolipram and Ro-1724 ((4-(3-Butoxy-4-methoxybenzyl)-2-imidazolidinone) (Ro-20-1724)), also known as XX5.

In issuing the rejection, the Examiner has contended that the present claims, which are directed to the administration of PDE4 inhibitors to treat CLL, are not enabled "in view of the well established unpredictability of treating chronic lymphocytic leukemia."

Applicant submits that this position ignores the present situation – applicants have identified agents that can treat CLL, namely PDE4 inhibitors, and have exemplified this with two species. Thus, applicant has provided ample evidence to support the use of PDE4 inhibitors to treat CLL. Indeed, the Examiner has acknowledged that the specification enables the two specific

PDE4 inhibitors. Applicant teaches that the class of PDE4 inhibitors is not unpredictable. And the science supports this teaching by showing that members of this class of inhibitors behave alike in a wide range of functional assays and their use to treat different conditions. Therefore, the teaching that members of this class will act in the same way in the treatment of CLL has not been refuted.

The Examiner has explicitly acknowledged that the applicant has provided **two enabling working examples** using the prototypical PDE4 inhibitors. Applicant demonstrated that both rolipram and XX5 (Ro20-1724), two different PDE4 inhibitors, work in the present invention. See Examples 4-6 at pages 18-22 and the accompanying figures. The specification also explicitly teaches that other PDE4 inhibitors will work, for example stating at page 22 that "[i]t is not intended that the present invention be limited to only one particular inhibitor."

Attached hereto is the Declaration of Dr. Adam Lerner, the inventor of the present invention. In his Declaration, Dr. Lerner indicates that a third PDE4 inhibitor, in addition to the two exemplified in the specification, is effective for the treatment of CLL, and provides that data. Dr. Lerner states that one skilled in the art would expect additional PDE4 inhibitors to be therapeutically efficacious for the treatment of CLL.

The class of PDE4 inhibitors has been the subject of intense research and development over the last ten years. PDE4 inhibitors first emerged as exciting potential therapeutics in the mid-1990s, largely because of their effects on several inflammatory/immunocompetent cells. Many of the early studies evaluated rolipram because it was prototypical, describing it as the "the **prototype PDE4 inhibitor rolipram**" (Teixeira et al., Trends in Pharmacological Sciences, 18(5): 164-71, 1997, p. 165 col. 1, ¶ 2, attached hereto as Exhibit 1; emphasis added). Numerous PDE4 inhibitors were known at the time, as detailed in Table 2 of Teixeira, and additional inhibitors have been developed. For example, three different PDE4 inhibitors are currently in advanced clinical trials

for the treatment of chronic obstructive pulmonary disease (COPD; Sturton et al., *Chest.* 2002;121:192S-196S; attached hereto as Exhibit 2); one of these (cilomilast) has been approved.

The functional similarity of PDE4 inhibitors is confirmed by Table 2 of Teixeira, which summarizes studies of the effects of PDE4 inhibitors in experimental models of inflammation *in vivo*. Part of this table is reproduced here, to illustrate that multiple PDE4 inhibitors have similar functions as taught. In the table excerpt, the following 6 different PDE4 inhibitors were successfully used to inhibit septic shock: **rolipram**, BRL61063, zardaverine, denbufylline, CP77059, and **R020-1724**. Strikingly, applicant notes that the exemplified compounds, rolipram and Ro20-174, behaved in a functionally similar manner to the other 4 PDE4 inhibitors. See also the Declaration of Dr. Lerner. Similarly, 3 different PDE4 inhibitors were successfully used to inhibit a different condition, acute respiratory distress syndrome: rolipram, zardaverine, and denbufylline, as shown in this table excerpt. Again, the "prototypical" inhibitor rolipram was functionally similar to other PDE4 inhibitors.

Yet another example of the functioning of PDE4 inhibitors is their suppression of the activation of inflammatory cells, which plays a critical role in both asthma and COPD. As shown in Table 2 of Teixeira, 8 different PDE4 inhibitors, including the two exemplified in the present invention, have similar functions in inhibiting antigen-induced immune cell reactions: **Rolipram**, CP80633, CDP840, RP73401, zardaverine, **Ro20-1724**, ORG20241, and CP77059.

Condition modelled	Species	Parameters measured	PDE4 inhibitor used	Route of administration	Effects observed
Septic shock	Mouse	Serum TNF-α, lethality	Rolipram, BRL61063	p.o./i.p.	Inhibition
	Mouse	Serum TNF-α, liver injury	Rolipram, zardaverine[a]	p.o.	Inhibition
	Rat	Bowel haemorrhage	Rolipram, denbufylline	i.p.	Inhibition
	Dog	Mesenteric hypoperfusion	Denbufylline	i.v. infusion	Reversal
	Rat	Serum TNF-α	Rolipram	i.v.	Inhibition
	Mouse	Serum TNF-α, LPS-induced lethality	Rolipram, CP77059	p.o.	Inhibit TNF-α at lower doses
	Mouse	Local and systemic TNF-α, levels	Rolipram	p.o.	Inhibition (locally is dependent on adrenal hormones)
	Mouse	Serum TNF-α, lethality	Rolipram, CP77059	p.o.	Inhibition (CP77059> rolipram)
	Rat	Renal blood flow, vascular resistance, glomerular filtration rate	Ro20-1724	i.v. infusion	Reversal of LPS-induced effects
Acute respiratory distress syndrome	Rat	Serum TNF-α, lethality, pulmonary oedema, liver injury, lung neutrophils	Rolipram	p.o.	Inhibition of all except pulmonary oedema
	Rat	Lung neutrophils, elastase activity and AHR	Zardaverinea	i.p.	Inhibition
	Rat	IL-2-induced pulmonary oedema, lung neutrophils, lung TNF-α	Rolipram	i.v.	Inhibition
	Guinea-pig	Lung oedema and neutrophils after aerozolised LPS	Rolipram, denbufylline	p.o., i.p.	Inhibition of all but lung neutrophilia

Table 2 | Teixeira et al.

Accordingly, applicant respectfully submits that there is ample evidence, both in the specification and in the art, supporting their teaching of the use of the class of PDE4 inhibitors to treat CLL and its exemplification with 2 members – rolipram and Ro20-1724; see also the Declaration of Dr. Lerner. The art amply demonstrates that members of the class of PDE4 inhibitors, including the two exemplified inhibitors rolipram and Ro20-1724, function similarly to treat conditions in which they have been shown to be effective.

Accordingly, based on the specification, including its extensive exemplification, the attached Declaration of Dr. Lerner, and the literature on the activity of numerous PDE4 inhibitors, the use of these inhibitors to treat CLL is enabled, and the rejection should be withdrawn.

In view of the foregoing, Applicant respectfully submits that all claims are in condition for allowance. Early and favorable action is requested.

In the event that any additional fees are required, the PTO is authorized to charge our deposit account No. 50-0850.

Respectfully submitted,

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